Wood (H.C.) & Cerna (D)

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Nitrous Oxide, Nitrogen, Oxygen,

AND

Carbonic Acid

UPON THE CIRCULATION,

WITH ESPECIAL REFERENCE TO

NITROUS OXIDE ANÆSTHESIA.

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A RESEARCH TO DETERMINE THE ACTION OF NITROUS OXIDE, NITROGEN, OXYGEN, AND CARBONIC ACID UPON THE CIRCULATION, WITH ESPECIAL REFERENCE TO NITROUS OXIDE ANÆSTHESIA.

PART I.

THE knowledge that we have of the physiological action of nitrous oxide indicates that it has no inherent anæsthetic properties, but that the loss of consciousness which follows its inhalation is the result of asphyxia. The arguments of this view are given in detail in Dr. H. C. Wood's "Treatise on Therapeutics," but may be summed up in a few sentences.

There not only is no proof that nitrous oxide has the power of yielding oxygen to the tissues of the body, but our present knowledge indicates that it escapes from the body unchanged.

Jolyet and Blanche, Elihu Thompson, and other investigators assert, as the results of experimental observations, *first*, that animals live no longer in an atmosphere of pure nitrous oxide than they do in one of nitrogen; *second*, that inhalations of pure nitrogen gas produce

symptoms similar to those of nitrous oxide narcosis; *third*, that the introduction of oxygen makes nitrous oxide entirely capable of supporting life indefinitely.

The experiments of Jolyet and Blanche indicate that the phenomena which are produced by the inhalation of nitrous oxide are not due to any accumulation of carbonic acid in the blood, but to the deprivation of oxygen, which, *a priori*, would seem to be logically inevitable, since the inhalation of nitrous oxide stops the formation of carbonic acid by cutting off the supply of oxygen; but, so far as our present knowledge goes, has no effect upon the throwing off of carbonic acid.

The French experimenters just named, in their analyses of the gases of the blood during nitrous oxide anæsthesia, found that there was less carbonic acid at the time when the animal was unconscious than when it was conscious, but that coma did not develop until the oxygen in the blood was reduced to three-fourths per cent. This result in turn was confirmed by the experiments of Dr. Amory, who found that immediately after the recovery of consciousness from nitrous oxide narcosis, less than one-third the normal amount of carbonic acid was given off from the lungs. When to these various facts is added the statement, based upon personal experiment of Dr. MacMunn, that the arterial blood of the animal killed by nitrous oxide affords only spectrum lines of reduced hæmoglobin, the nature of nitrous oxide anæsthesia seems to be well established.

The assertion of Krishaber, however, that the circulation is affected very differently by

the inhalation of nitrous oxide by mechanical asphyxia, seems to be contradictory to the other evidence, and has led the authors of the present paper to make an investigation of the subject.

Our first experiments were directed especially to a study of the changes in the pulse and blood-pressure produced by the inhalation of pure nitrous oxide. In discussing the experimental results obtained with nitrous oxide gas, we shall direct the attention of the reader, *first*, to the time which elapsed between the commencement of the inhalation and the development of complete anæsthesia; *second*, to the effect of the drug upon the rate and character of the pulse; *third*, to its influence upon the blood-pressure.

Anæsthesia.—The test which we employed to determine the presence of complete anæsthesia was the conjunctival reflex. When this was completely abolished, the animal was said to be completely anæsthetized. There were so many matters to be attended to in detail in these experiments, that it is entirely possible that in some cases the corneal reflexes may have been abolished a few seconds before a note of their non-existence was taken by us. It is certain, however, that in no case were the reflexes noted as abolished before they were completely gone. It is, therefore, very possible, indeed probable, that some of our periods are too long, but it is not possible that any of them are too short. The length of time which we found to elapse between the commencement of inhalation and anæsthesia varied from fifty-one seconds to three minutes and fifty seconds. In three out of the seven inhalations it was less

than two minutes; in only one inhalation did it distinctly exceed two and a half minutes. The average period was two minutes and eight seconds.

Pulse.—In our first experiment (Experiment 1) the inhalation of nitrous oxide was immediately followed by an enormous rise of the arterial pressure, associated with great disturbance of the pulse; the heart-beats became very irregular, with long diastolic pauses, some of them lasting several seconds, followed by a number of very rapid pulse-beats.

The animal (dog) was allowed to recover consciousness completely, and several minutes later the second inhalation was begun. Owing to a slipping of the canula there had been some loss of blood from the arterial system. The pulse-rate was 144 a minute; in ten seconds it fell to 108 a minute; in ten seconds more to 96 a minute. Then it began to rise, reaching, in the course of twenty seconds, 120 a minute, at which point it stayed until the gas was withdrawn.

In Experiment 2 the pulse-rate was slightly slowed, almost directly after the inhalation, but a pronounced descent did not take place until nearly one minute had elapsed, when the pulse rapidly fell to about one-third of its original number, with heart-beats which were most extraordinary in their power and in the size of the wave which they gave rise to. At the same time, when anæsthesia was noted as complete, the pulse was about 60 beats to the minute slower than it had been originally. It continued to fall, and fifty seconds later was below one-half its norm. Respiration at this time had become very distant and irregular.

After the respirations had entirely ceased, and the animal, so far as respiration was concerned, was dead, the pulse-rate was about one-half of what it had been. The pulse-waves were two or three times as large as before the inhalation, this, too, although the arterial pressure had fallen almost to zero. The second inhalation in this experiment was made four or five minutes after the animal had regained complete consciousness from the previous inhalation. The pulse was at this time slowed to 108 a minute; but, nevertheless, while under the influence of the gas, fell steadily, being only 60 a minute at the time the respirations had been so reduced in number that they only recurred at intervals of ten to fifteen seconds.

In Experiment 3 the phenomena of the pulse were similar to those of Experiment 2, the pulse-rate falling at first very slowly and afterwards very rapidly, so that at the end of one minute and forty seconds it was less than one-half of what it had been. It then rose temporarily, but at the time when artificial respiration became necessary to keep the animal alive, it had fallen considerably below one-half the rate it previously had been.

In Experiment 4 the pulse kept at about the rate it was before the inhalation for about a minute and a half, when it began to fall in a peculiar, very irregular way, and at the time of complete anæsthesia it was a little under one-half of its normal number, and though it varied after this somewhat in the rapidity of its beat, by the time the respiratory centres were so paralyzed that it was necessary to supply artificial respiration to restore the ani-

mal, the pulse-beat was 60 a minute. When the pulse had become this slow, the size of the individual pulse-wave was enormous,—seven or eight times its original size. The second inhalation was made some minutes after the complete restoration of the animal to consciousness. It was followed after thirty seconds by a decided fall in the rate of the pulse, and at the end of a minute the pulse was only one-half what it had originally been. When anæsthesia was complete, the pulse was considerably under one-half of its normal in frequency. This inhalation was kept up until death, and although at the last the pulse became distinctly much more frequent, it never reached a rate equal to the norm; a few seconds before death, when the arterial pressure was less than half its original height, the pulse-wave was twice as large as the norm.

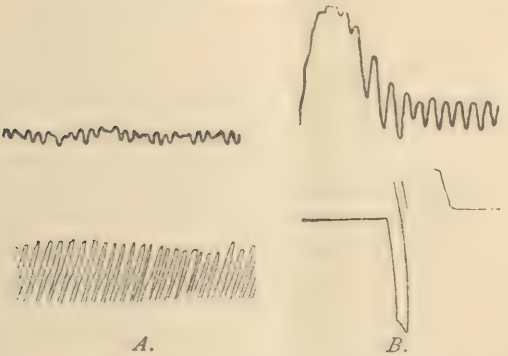
In their general results, so far as the effect of the inhalation of the nitrous oxide upon the pulse is concerned, the experiments which we have detailed are concordant. In one instance there was a stormy irregularity of pulse, but usually under the influence of the gas the pulse falls very decidedly in number, while the individual pulse-beat or arterial wave is enormously increased in size.

In order to show clearly this peculiar pulse change, we append here tracings taken from one of our experiments, showing the highest size of the pulse-wave before inhalation and its size during a portion of the period of anæsthesia. (See Fig. 1.)

In order to determine whether the slowing of the pulse caused by nitrous oxide is due to an action upon the inhibitory centres, the gas

was given to a dog whose vagi had been previously divided. Before the inhalation the

FIG. 1.



EXPERIMENT 4.—*A*, tracing before inhalation. *B*, tracing when animal was profoundly anæsthetized and respirations reduced to 7 to 10 a minute. Tracing shows second marks; respiration, abscissa line.

pulse ranged from 150 to 160; five seconds after the inhalation it was 165; fifteen seconds after this it was 200. Shortly after this the animal had such severe convulsive struggles that the tracing is excessively irregular, but in about forty seconds more, or a minute after the inhalation had been entered upon, the pulse was 241 a minute. Half a minute later it was 204, half a minute later 228, one minute later 180, and thus it continued above the original point until the death of the animal. Throughout the whole course of this experiment the pulse-wave was exceedingly small.

This experiment shows that the slow, huge pulse, so characteristic of the action of nitrous oxide gas, is absent when the pneumogastrics

have been previously divided, and that it is, therefore, due to stimulation of the inhibitory cardiac apparatus.

Blood-Pressure.—The effect of the inhalation of nitrous oxide on the blood-pressure varied somewhat in the different experiments.

In Experiment 1, in both the first and second inhalations, there was an immediate and enormous rise of the blood-pressure, this rise amounting in the first inhalation to one hundred and twenty millimetres in one minute and twenty-two seconds after the commencement of the inhalation. In the second inhalation, the rise in a minute and twenty seconds was about sixty millimetres.

In Experiment 2 the blood-pressure went up moderately,—that is, about ten millimetres in twenty seconds,—and maintained itself at this position for about a minute, when it commenced to fall, getting below the norm, but recovering itself, so that by the time the anæsthesia was complete the blood-pressure was the same as in the commencement of the experiment. The continued inhalation of the gas was followed by a steady fall in the arterial pressure, which was almost at zero. Artificial respiration was used to resuscitate the animal, which had long ceased to breathe. The second inhalation produced alterations in the circulation similar to but much less pronounced than those of the first experiment. There was a slight rise of pressure, followed by a fall, so that the blood-pressure was below the norm when the conjunctival reflexes were first noticed to be abolished. After this there was a remarkable rise in the pressure, which did not, however, quite reach the norm, and, after a

time, fell again, until it was near the zero point.

In Experiment 3 the blood-pressure rose very slightly,—that is, four millimetres after the inhalation had commenced,—and kept at about this point for half a minute longer, when it commenced to fall, and when the conjunctival reflexes were noted to be abolished the arterial pressure was twenty millimetres below the norm. From this point it fell, with occasional momentary rises, until artificial respiration was resorted to to restore the animal, at which time the pressure was about fifty-five millimetres below the original.

In Experiment 4 the inhalation was followed by a rise at the end of one minute of about twenty millimetres. The blood-pressure continued to increase with occasional fluctuations, so that by the time anæsthesia was complete it was about sixty millimetres above the norm. It then commenced to fall, but when the gas was removed and artificial respiration employed, was still far above zero.

In the second inhalation there was a rise in one and a quarter minutes of about thirty centimetres; the blood-pressure after this steadily increased, so that by the time the conjunctival reflexes were noted to be abolished the pressure was eighty centimetres above the norm. After this it fell, with occasional paroxysms of rising until about a minute before death, when it commenced to fall very rapidly and steadily towards zero.

In Experiment 5 the arterial pressure rose after the inhalation about thirty centimetres, and then very slowly fell.

The extraordinary rise in arterial pressure

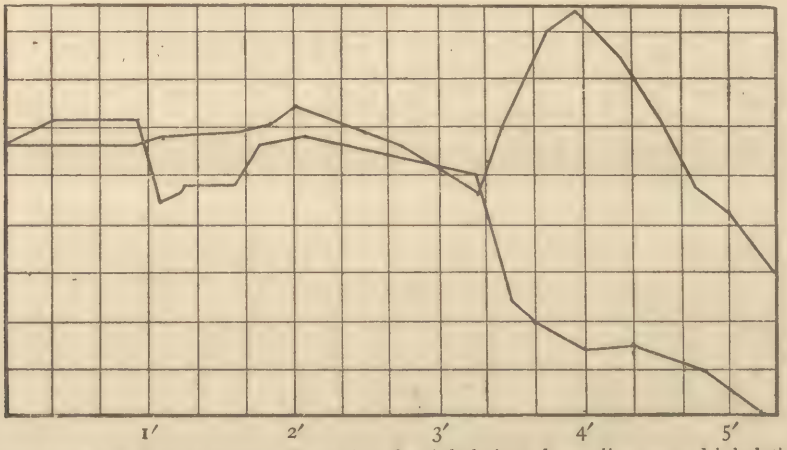
which took place in some of our experiments during the inhalation of nitrous oxide gas has an important bearing upon practical medicine.

Some time since a death from apoplexy occurred in Philadelphia, directly after the inhalation of nitrous oxide, and it is well known that Dr. Lafont, of France, has asserted that occasionally diabetes mellitus and albuminuria have been produced by the anæsthetic use of nitrous oxide. It is entirely conceivable that in a man with atheromatous or otherwise diseased arteries the inhalation of the gas might cause a rise in the arterial pressure which should produce rupture of smaller or larger vessels, and cause serious symptoms.

In order to portray the effects of nitrous oxide upon the blood-pressure, we have prepared the series of curves which we herewith append, each curve representing the line of average blood-pressure of a single continuous inhalation.

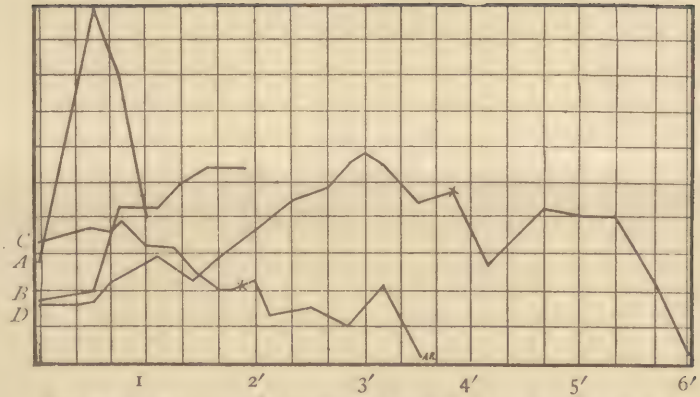
An examination of the diagrams will show, what is revealed even more clearly by our original tracings, that after the inhalation of nitrous oxide gas there is almost always a rise in the arterial pressure, which rise varies very greatly in its extent, as well as in the rapidity of its occurrence. Sometimes it is immediate and excessive; usually, however, it is slowly produced and only moderate in extent. In some cases it occurs a considerable time before the abolition of the conjunctival reflexes, while occasionally its coming on is postponed until after the disappearance of the eye reflexes. In all our experiments, if the inhalation continued, the blood-pressure finally began to fall, and at last reached the zero line; always, however,

FIG. 2.



EXPERIMENT 2.—Nitrous oxide. Upper line, first inhalation; lower line, second inhalation.

FIG. 3.



NITROUS OXIDE.—Arterial pressure. Experiment 1 : *A*, first inhalation ; *B*, second inhalation. *C*, Experiment 3. *D*, Experiment 4.

the pressure was well maintained until long after the complete cessation of respiration, the animal dying through the respiration and not through the heart. Indeed, the maintenance of the circulation after the practical paralysis of the respiratory system is very remarkable. It is also of very great importance in relation with practical medicine. Chloroform directly depresses the heart, and even ether has a similar influence when it is in excess, but nitrous oxide would appear, directly or indirectly, to stimulate the heart and to keep up this stimulation at a time when the respiratory function is almost completely obliterated. A lost respiratory function can be temporarily replaced by artificial respiration, but we have no substitute at all for an arrested heart. It is easy to see why death has so very rarely occurred during anæsthesia from nitrous oxide.

In order to determine whether the rise of arterial pressure produced by nitrous oxide be due to vaso-motor spasm or not, one experiment was made upon an animal (Experiment 6) whose spinal cord had been divided above the origin of the splanchnic nerves. The result of the inhalation of the nitrous oxide was an immediate and very pronounced fall in the arterial pressure. This would seem to indicate that the rise of the arterial pressure usually caused by the gas is due to vaso-motor spasm, but undoubtedly such spasm is accompanied by a very pronounced increase in the force of the heart's beat. To determine whether the fall of the arterial pressure, which occurs late in the inhalation, is due to vaso-motor paralysis or not, a very powerful current was applied

to the sciatic nerve of the animal (Experiment 7), whose arterial pressure had fallen, under the influence of the nitrous oxide, from 138 to 120. After ten seconds of application of the current, the pressure was 109. About half a minute later the arterial pressure was 110, and when the current had been applied about twenty seconds the arterial pressure stood at 103. The faradization of the nerve was always accompanied by a violent tetanic spasm of the tributary muscles, showing that at least the motor fibres of the nerve were capable of transmitting impulse. In each instance the pressure fell rather than rose. The pulse-waves were extraordinarily large, and the heart evidently putting forth enormous effort. The pneumogastrics had not been severed, but the irritation of the nerve had no effect upon the pulse-rate, so that there was no reflex inhibition of the heart to interfere with rise of the arterial pressure. The failure of irritation of a nerve to cause rise of pressure shows that at this time the vaso-motor system was unable to respond to peripheral stimuli, and warrants the conclusion that the fall of arterial pressure which occurs in the advanced stage of nitrous oxide anæsthesia is due to vaso-motor paralysis.

The experiments which we have made with nitrous oxide gas prove that the characteristic effects of the inhalation upon the circulation are: slowing of the pulse, accompanied by a pronounced increase of energy in the single heart movement, and extraordinary increase of the size and force of the pulse-wave, and followed very late in the poisoning, after the failure of respiration, by excessive rapidity and feebleness of the pulse; primary rise of the

arterial pressure of variable extent, followed after a time, and often after unexplained vicissitudes of pressure, by a progressive fall of pressure to zero. The chief cause of the rise and fall of pressure has been shown to be vaso-motor stimulation and vaso-motor paralysis, while the slowing of the pulse is due to stimulation of the inhibitory apparatus.

At this juncture the question naturally offers itself to us for solution, "Are these changes which we have seen due to an indirect or direct action of the nitrous oxide?"

In examining into this subject we first made experiments to determine whether the administration of a small amount of oxygen, along with the nitrous oxide, would prevent the development of anæsthesia. Atmospheric air contains twenty per cent. of oxygen, and we had prepared thirty gallons of a mixture containing one-half this proportion of oxygen,—*i.e.*, ninety per cent of nitrous oxide, ten per cent. of oxygen. This was administered by inhalation to a moderate-sized dog (Experiment 8). The whole of the gas was used up in eight minutes, and neither at the end of this period nor at any time during the inhalation was there the slightest anæsthesia.

Ten per cent. of oxygen is, therefore, capable of suspending the anæsthetic action of nitrous oxide.

The action of the nitrous oxide upon the pulse was, however, not suspended. Before the inhalation the pulse varied from 120 to 130; in twenty seconds after the inhalation it had fallen to 108; in twenty seconds later to 84; some seconds after, it was below 80, when for some reason it rose nearly to the norm, and

remained at this position nearly half a minute, when it fell very suddenly to about 50, and remained about this rate until the end of the inhalation.

The arterial pressure before the inhalation varied in its average from 148 to 155; thirty seconds later it was 150; forty seconds later it was 145; thirty seconds later it was 149; thirty seconds later, 140; thirty seconds later, 157; thirty seconds later, 158; thirty seconds after this, 150; and about at this figure it continued until the end of the experiment.

This experiment appears to show that the addition of ten per cent. of oxygen suspends the anæsthetic effect of nitrous oxide, as well as its influence in raising the blood-pressure, but not its power of reducing the pulse-rate by inhibiting the heart.

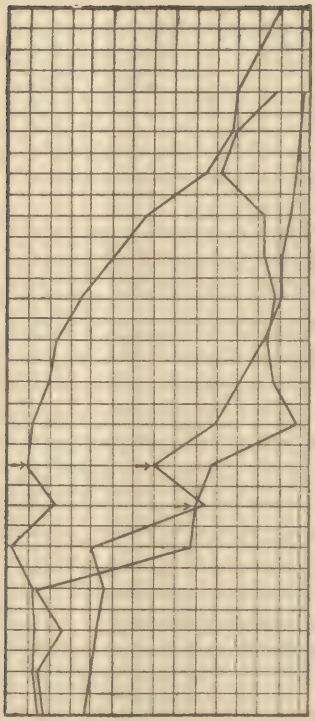
The conclusion that the anæsthetic and vaso-motor influence of nitrous oxide are in some way apart and separate from its action upon the pulse would appear to receive confirmation from the experiments made upon nitrous oxide by itself. The influence of nitrous oxide upon the pulse was very uniform in the different experiments, and consistent throughout the single experiment, while its influence upon blood-pressure was not only very different in the different experiments, but also varied very curiously and unaccountably in the one experiment, the blood-pressure rising and falling without any obvious rhyme or reason. It would look as though nitrous oxide acts upon the heart and nervous system directly, but has little or no direct inherent influence upon the vaso motor centres or the brain cortex.

The experiments with nitrogen are three in number. In the first experiment (Experiment 9) unconsciousness was complete one minute and ten seconds after the beginning of the inhalation, but it may have been present before this time. Death occurred three minutes after the beginning of the inhalation of the gas; the arterial pressure was raised in forty seconds twelve millimetres; during the next ten seconds it went up to ten millimetres more, and then fell abruptly eighty to ninety millimetres in the next ten seconds, and continued to fall until death.

In the second experiment (Experiment 10) consciousness was completely lost one minute after the beginning of the inhalation. The arterial pressure slowly rose, reaching its maximum forty seconds after the beginning of the inhalation, when it had gone up fifteen millimetres. After this it fell slowly for a time, and then rose again, one minute and a half after the beginning of the inhalation being a little above the point at which it had started; it then fell, at first slowly, and afterwards more rapidly, until death, which occurred three minutes and ten seconds after the beginning of the inhalation.

In the third experiment (Experiment 11) the pressure at first descended a little, and then rose again, so that forty seconds after the beginning of the inhalation it was three millimetres below its starting-point. After this it fell, at first slowly, and then rapidly, until death, which occurred two minutes and forty seconds after the beginning of the inhalation. In this experiment unconsciousness

FIG. 4.



EXPERIMENTS 9, 10, 11.—Inhalation of Nitrogen.

occurred exactly one minute after the beginning of the inhalation.

In each of the experiments with nitrogen the pulse was at first more or less increased in frequency, and afterwards became slower, usually continuing so until death. The pulse-waves were also markedly increased in size, being, even when the pressure had almost reached zero, much greater than in the normal animal.

These experiments show that during the inhalation of nitrogen there is usually a slight rise in the arterial pressure, followed by a fall, and accompanied by primary increase of the pulse-rate, which increase varies very much, and is followed by a secondary fall.

In contrasting the results which we have obtained with nitrogen and with nitrous oxide, our experiments would seem to show that anæsthesia is produced more rapidly when nitrogen is used than when nitrous oxide is inhaled; but, in reviewing the details of our work, we are led to suspect that in some of our experiments with nitrous oxide, owing to a leak in a valve, a little air got mixed with the gas, and thereby delayed the coming on of unconsciousness. Further, as has already been stated, in some of the experiments with nitrous oxide, anæsthesia may have been developed before it was noted. When to these facts are added the circumstance that our experiments with nitrous oxide were much more numerous than those with nitrogen, and that in several cases anæsthesia was produced by nitrous oxide more quickly than in any of our experiments with nitrogen, we do not think that nitrogen can be considered to be a more rapid anæsthetic than nitrous oxide.

The changes in the circulation produced by nitrogen and nitrous oxide differ in quality rather than in kind. In each agency there is a tendency to a rise of pressure, followed by a fall, the rise of pressure being much less with nitrogen than with nitrous oxide. The pulse was, on the whole, similarly affected by the two gases, a strong indication that the action of nitrous oxide upon the pulse is, after all, rather indirect than direct.

Our experiments, therefore, indicate a parity of action between nitrogen and nitrous oxide, and make it very probable that the two agencies act in a similar manner,—that is, by shutting off oxygen.

The blood-changes which are produced by the inhalation of nitrous oxide or nitrogen resemble those caused by mechanical asphyxia, although they are not identical. The rise of pressure is usually much greater in mechanical asphyxia than during the inhalation of either of these gases, but by a number of experiments we have found that even when the trachea is hermetically sealed the amount and duration of the circulatory disturbance varies remarkably, being in some cases very much greater than in others.

It seems to be that *a priori* it might be expected that the changes of the circulation produced by the inhalation of the inert gas should resemble in kind those caused by mechanical arrest of respiration, but should not be identical with them. The mere stoppage of the passage of gas in and out of the lung, and the consequent violent efforts of breathing, must have some influence upon the peripheral nerve filaments in the lungs, which influence would, in

turn, react upon the centres of respiration and circulation. Moreover, the gases in the blood differ when the respiration is mechanically arrested from those which follow the inhalation of an inert gas. Under the latter circumstance there is no check of the throwing off of carbonic acid from the blood, although the formation of carbonic acid gas is arrested; in mechanical asphyxia the throwing off of carbonic acid from the blood is put an end to; consequently, while in mechanical asphyxia there is accumulation of carbonic acid in the blood, in the asphyxia caused by an inert gas the carbonic acid in the blood becomes less than normal. Both mechanical and gaseous asphyxia result in the lessening of the oxygen of the blood. In this, and in this only, so far as the gaseous conditions of the blood are concerned, the two processes have a common effect.

The changes in the circulation produced by the inhalation of nitrous oxide or of nitrogen resemble somewhat those caused by mechanical asphyxia. Certainly any differences which may exist are not of sufficient foundation for any argument that nitrous oxide and nitrogen act as direct anæsthetics, or, in other words, as substances which deprive animals of consciousness by virtue of properties inherent in themselves. The similarity in the action of the two gases, both as to the general symptoms which they cause and as to the circulatory changes which they produce, is striking, and indicates distinctly that they have a common action. The action of nitrogen is certainly simply that of an inert substance which shuts out oxygen, and the whole mass of evidence is concordant in showing that the anæsthesia pro-

duced by the inhalation of nitrous oxide is due to the shutting off of the supply of oxygen from the nerve-centre.

Our research upon nitrous oxide might well have ended at this point, but the results reached have suggested the propriety of determining the effects of an excess of oxygen and carbonic acid upon the blood-pressure.

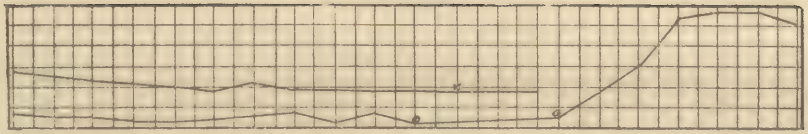
PART II.

THE first series of experiments in the second part of this research was made to determine the effect in the inhalation of oxygen upon the pulse and arterial pressure.

In the first of these experiments (Experiment 12), after the inhalation of pure oxygen gas for two minutes, the pulse was four beats per minute below its starting-point, and the arterial pressure three millimetres below its starting level. In Experiment 13 the pulse, at the end of four minutes of inhalation, had been reduced eight beats, while the blood-pressure had fallen four millimetres. That even this slight fall of pulse and blood-pressure was not directly the outcome of the action of the oxygen, but was due to indeterminable circumstances, is shown by the fact that, the inhalation being continued, one minute and forty seconds later the pulse was two beats per minute more than at the start, while at the end of the two minutes and forty seconds the pressure was one millimetre above its original place. In Experiment 3 the pulse, after three and a half minutes of inhalation, was three beats per minute higher than at the start, and the blood-pressure two millimetres.

These experiments certainly show that the inhalation of pure oxygen gas has no influence upon the circulation, and would seem to warrant the conclusion that oxygen gas has no di-

FIG. 5.



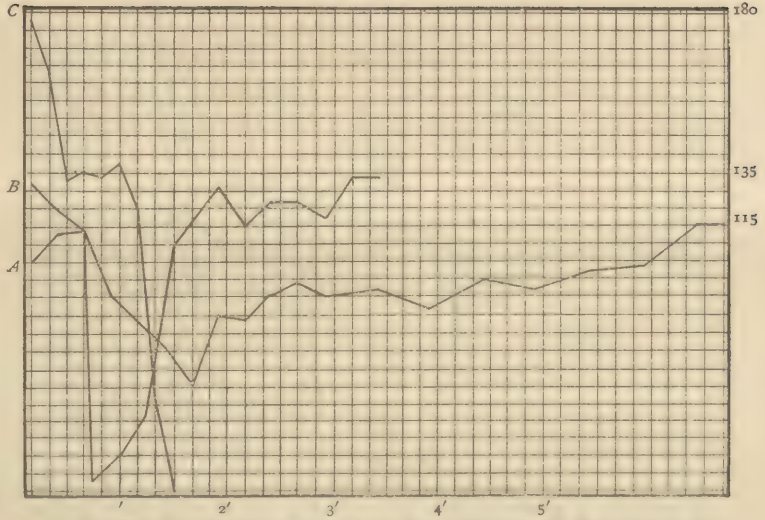
OXYGEN.—Curve showing the changes in the blood-pressure during two prolonged inhalations of pure oxygen. The sudden rise in the pressure at the end of the second line was due to a mechanical arrest of respiration.

rect influence upon the circulation, and that, therefore, the fall of pressure produced by excessively rapid and forced respiration is the result of the pumping out of the blood of carbonic acid, rather than of any increase in the oxygen of the blood, while the rise of the arterial pressure in asphyxia is due to the presence in the blood of an excess of carbonic acid.

The conclusion just reached naturally led up to a direct experimental study of the effect of carbonic acid upon the arterial pressure. In carrying out such study we have made several series of experiments.

In the first series the animal was made to breathe *pure* carbonic acid. In the first experiment (Experiment 14) the reflexes were completely abolished in thirty seconds; the arterial pressure fell in fifteen seconds twelve millimetres, remained at about this point for fifteen seconds longer, when it slowly began to rise, and in fifty seconds more was five millimetres above its norm; it then rapidly fell again, so that in thirty seconds later it was sixty millimetres below the norm. The animal was then allowed to recover consciousness and to rest for ten minutes; after this it was given a second inhalation of the gas, which was followed by a slight rise of the pressure, so that in thirty seconds, when the reflexes were gone, the arterial pressure was seven millimetres above the norm; then the pressure dropped rapidly,—in fifteen seconds twenty-two millimetres, in thirty seconds forty-eight millimetres; then for a few seconds it remained steady, but soon recommenced to fall, and in one minute and fifty-five seconds after the beginning of the inhalation had reached almost

FIG. 6.



CARBON DIOXIDE.—*A* represents first inhalation of Experiment 14; *B* represents first inhalation of Experiment 15; *C*, second inhalation.

to the zero line; fifteen seconds later the animal was dead.

In Experiment 15, with pure carbonic acid, the inhalation of the gas was followed by an immediate, rapid, and steady fall of the arterial pressure, which reached its maximum in a minute and a half; after this time the pressure began to rise, but failed to reach its norm during the inhalation. In this experiment it was evident that the animal obtained some air mixed with the gas, for at the end of seven minutes the pressure was well maintained; the valve used in the mouth-piece was subsequently found to be leaky, and without doubt air passed through it during inhalation. The second inhalation was in this case followed by an immediate and rapid fall of pressure, zero being reached in about a minute and a half.

In Experiment 16 the conjunctival reflex was completely gone after thirty seconds of inhalation. The arterial pressure fell for thirty seconds, then rose to a little above the norm, but about a minute and a quarter after the beginning of the inhalation began to fall and rapidly lowered, so that one minute and forty-five seconds later it was about sixty millimetres below the norm. After ten minutes of consciousness a second inhalation was followed by complete abolition of reflexes in thirty seconds, and, after a brief primary rise by a steady but somewhat irregular fall of pressure, zero and death being reached in a little less than two minutes.

In order to give a better idea of these changes, Dr. Cerna has plotted them as given below.

In Fig. 6 the line *A* represents the first

inhalation of Experiment 14, the second not being plotted; the line *B* represents the blood-pressure in the first inhalation of Experiment 15; *C*, the second inhalation.

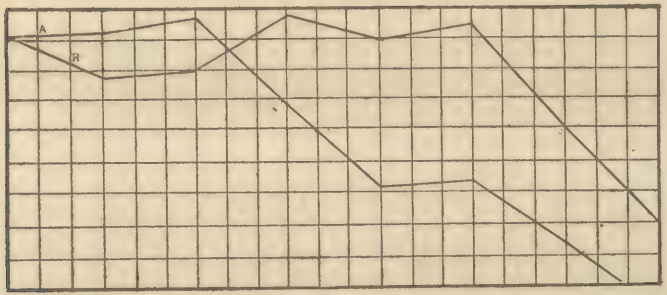
Figure 7 represents Experiment 16. *A* the first, *R* the second inhalation.

The tracings in these experiments vary so much as to indicate that in some of them air got in with the carbonic acid. We, therefore, made the following experiments with a mercurial valve, so arranged that leakage was impossible.

In Experiment 17 the inhalation of pure carbonic acid was followed by an immediate and progressive, although irregular, fall of the arterial pressure. In forty-five seconds the pressure was twenty-eight millimetres below the norm; in one minute, fifty-seven millimetres; in one minute and a quarter it was sixty-two millimetres; and in one minute and a half, one hundred and two millimetres below the norm. Death occurred one and three-quarter minutes after the beginning of the inhalation. The result obtained in Experiment 18 was similar. In seventy seconds the pressure fell eighty millimetres, but after that it was nearly stationary, or even rose a little for fifty seconds, when it began again to slowly fall, and in twenty seconds more was one hundred and eight millimetres below the norm. Death occurred in one minute and a half after the beginning of the inhalation.

The effects of pure carbonic acid upon the arterial pressure are usually to lower it with more or less steadiness until death is attained. It has seemed to us very probable that diluted

FIG. 7.



EXPERIMENT 16.—*A* and *R* represent, respectively, first and second inhalations.

carbonic acid may increase arterial pressure, although, when in overwhelming amount, the gas depresses the pressure.

We have, therefore, made a series of experiments with carbonic acid diluted with known proportions of oxygen or air. The first of these two sets of experiments are those in which carbonic acid and oxygen were employed.

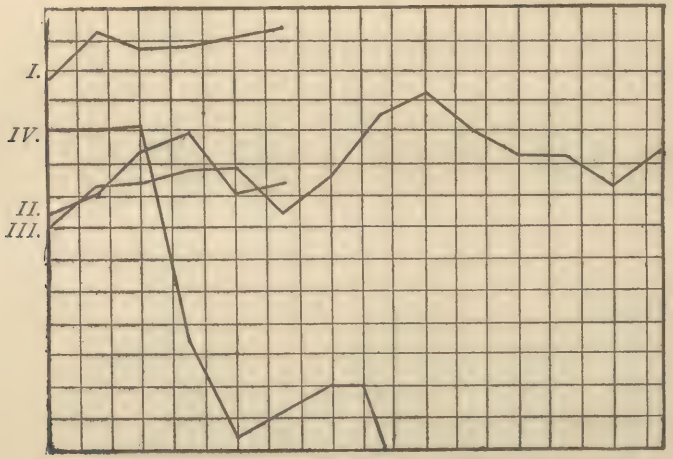
In Experiment 19 the inhaled gas contained 66.66 per cent. of carbonic acid and 33.33 per cent. of oxygen. The effect is shown in the following columns:

Beginning of inhalation.	Norm—N.
15 seconds.	N.
30 seconds.	N. + 10 m.
45 seconds.	N. + 6 "
1 minute.	N. + 31 "
1.30	N. + 52 "

In a second inhalation the arterial pressure rose in one and a quarter minutes to ten millimetres.

In Experiment 20 the first inhalation was made with a mixture containing sixty-four per cent. of oxygen and thirty-six per cent. of carbonic acid; in half a minute the pressure rose eleven millimetres, in one minute thirteen millimetres, in one minute and twenty seconds fourteen millimetres. In a second inhalation, a mixture containing 66.66 per cent. of oxygen and 33.33 per cent. of carbonic acid was used; in half a minute the arterial pressure rose twenty millimetres, but in half a minute more the pressure was only six millimetres above the norm. A third inhalation, after the animal had completely regained consciousness

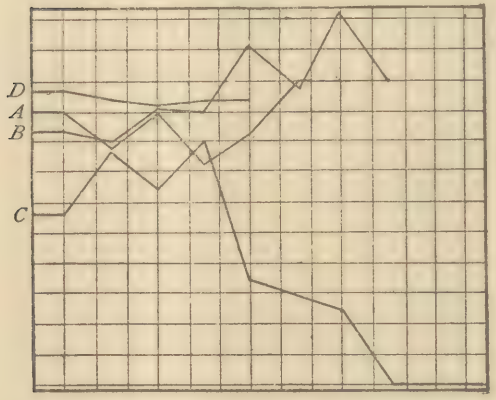
FIG. 8.



EXPERIMENT 20.—*I.*, inhalation, carbonic acid alone. *II.*, inhalation. *III.*, inhalation, each one-third oxygen. *IV.*, inhalation.

and had been allowed to rest fifteen minutes, was practised with the same mixture as was used just before. The result was a rise in thirty seconds of eleven millimetres, in one minute of eighteen millimetres, in one minute and a half of fourteen millimetres. The animal was then allowed to breathe air, but before consciousness was regained, violent con-

Fig. 9.



Experiment 21.—*A*, first inhalation of $CO_2 + 2O$. *B*, second inhalation of $CO_2 + 2O$. *C*, CO_2 alone, perhaps with a little O in it. *D*, O pure.

vulsions, with great rise of the arterial pressure, occurred. After a rest of fifteen minutes an inhalation of pure carbonic acid was given; half a minute later the pressure was practically unchanged, but in the next fifteen seconds it fell sixty-five millimetres, and continued to fall irregularly, so that two minutes after the beginning of the inhalation it was one hundred and twenty-six millimetres below its

starting-point; a few seconds after this death occurred.

In Experiment 21 we administered by inhalation at first a mixture containing 66.66 per cent. of oxygen and thirty-three per cent. of CO_2. At the first trial the pressure rose in thirty seconds seven millimetres, in one minute twenty-six millimetres, in one and a half minutes thirty-eight millimetres, the rise not, however, being a steady one. Some minutes later a second inhalation failed to produce effect equal to that previously obtained; after thirty seconds the pressure was unchanged, and in one minute it had only risen ten millimetres. After complete recovery from these inhalations the animal was given pure carbonic acid, and very shortly went into general convulsions, with great rise of pressure, followed by a rapid fall so soon as the convulsions ceased. Some time after the animal had regained its normal state it was made to inhale oxygen, the result being *nil* so far as the arterial pressure was concerned.

The experiments made with carbonic acid and air are two.

Experiment 22.—The mixture contained twenty-five per cent. of carbonic acid. The result was a slight rise of pressure, followed by a fall, as shown in the following columns:

Time.	Pressure.	
0	Norm.	Inhalation begun.
30	N. + 6	
1	N. + 16	
1.30	N. + 8	
2	N. + 10	

Experiment 23.—The mixture inhaled con-

tained twenty per cent. of carbonic acid; in forty-five seconds pressure rose ten millimetres; in a second inhalation of the mixture, containing ten per cent. of carbonic acid, there was a rise, followed by fall, as shown in the following columns:

Time.	Pressure.	
0	Norm.	Inhalation begun.
30	N. + 7	
1	N. + 2	
1.30	N. + 2	
2	N. + 1	
2.30	N. + 2	

As a result of all our experiments upon the subject, we think that the following proposition is established: Carbonic acid, when breathed into the lungs alone, sometimes causes a slight and temporary rise in the arterial pressure, but usually at once, and always after a very short time produces a very decided fall of arterial pressure; carbonic acid, when taken properly diluted, distinctly increases the arterial pressure, apparently having the most power when mixed with oxygen in the proportion of two to one.

Though generally concordant, our results vary so much as to suggest that carbonic acid has a double action; that by stimulating the vaso-motor centre it acts to increase the pressure, while by inhibiting the heart it acts to lessen the pressure.

This naturally brings us to a study of the action of the gas upon the pulse.

The effect of C_2O upon the pulse is very pronounced.

Thus in Experiment 14 the pulse fell from

120 to 64, and in the second inhalation from 120 to 44; in the first inhalation the pressure being low, in the second high.

In Experiment 15 pulse fell from 120 to 36.

In Experiment 16 pulse fell from 135 to 40.

With mixture the effect was similar. In Experiment 20, C_2O, sixty-four per cent.; O, thirty-six per cent.; pulse fell from 140 to 62. In Experiment 21, C_2O, sixty-six per cent.; O, thirty-three per cent.; pulse fell from 156 to 44.

It must, therefore, be allowed that carbonic acid acts very powerfully as a pulse depressor.

The probabilities from the evidence already given are very strong that the rise of pressure and the fall of pulse are respectively due to stimulation of the vaso-motor and cardiac inhibitory centres, and to obtain positive knowledge we made the following experiments:

The first series of experiments were made upon dogs with vagi cut.

In Experiment 24, after the pulse, section of the pneumogastrics, when the inhalation was begun, was 156 per minute, and suffered no change from this rate for thirty seconds, when the respiration became stormy, and the enormous respiratory blood-curves so dominated the small pulse-waves that the latter cannot be counted in the tracing; thirty seconds later there was a rapid fall of the arterial pressure, accompanied by quick breathing and a return of the pulse to about 160.

In Experiment 25, both vagi being cut, the pulse before the inhalation was 120 to 140; ten seconds later it was unchanged; a few seconds after this there was developed a period of violent respiration, occasional respira-

tory curves of the pulse, with disappearance of the pulse-waves from the tracing. The dog was then allowed to recover consciousness. After the pulse had returned to its normal rate a second inhalation was given, which was followed in a very short time by the reappearance of enormous respiratory curves, and the disappearance from the tracing of individual pulse-beats. This condition continued until death, which occurred from failure of the heart.

In Experiment 26, the pulse, after section of the vagi, was 180. The inhalation of carbonic acid was followed by rapid fall of pressure, and twenty seconds afterwards the pulse was 200 and the pulse-wave excessively small; thirty seconds later the pulse was 120, but it subsequently fell, just before death, to 100.

In Experiment 27, the pulse, after the section of the vagi, was 189. Inhalations of equal parts of air and carbonic acid were given, when the pulse rose in frequency, in half a minute being 240, and from this time varying during the continuance of the inhalation between 225 and 270. After this inhalation the animal was allowed to recover consciousness, and when the inhalation of pure carbonic acid was commenced the pulse was about 220; ten seconds later the respiratory curves so dominated the pulse-curves as to make the counting of the pulse-wave very difficult, but there seemed no change in the pulse. During the continuance of the inhalation, up to the time of death, the pulse-waves remained so minute that most of the time they could not be counted on the tracing, but fifty seconds after the commencement of the inhalation, the

pressure being extremely low, the pulse was for a little while distinct enough to be counted at 200 a minute.

These experiments are substantially concordant in showing that, after section of the vagi, the inhalation of carbonic acid does not produce distinct slowing of the pulse. The contrast between the effects of the inhalation, without and with sections of the vagi, upon the pulse-wave is very great. Usually after the pure gas the individual pulse-wave in the animal is extraordinarily increased, while in the animal whose vagi has been cut, the pulse-wave, after the inhalation, becomes exceedingly small, or, in most cases, entirely obliterated.

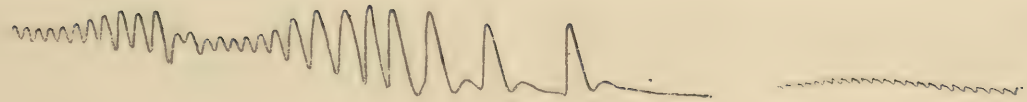
In order to show this contrast, we append two tracings, both of them taken just before death, No. 1 with the vagi uninjured, No. 2 with the vagi cut.

In conclusion, we believe that our experiments definitely prove that the large slow pulse produced by the inhalation of carbonic acid gas is due to stimulation of the vagi.

The second series of experiments was made to determine whether the rise of blood-pressure caused by carbonic acid gas is or is not due to an influence upon the vaso-motor system.

In Experiment 28 the cord was cut between the lower cervical and the first dorsal vertebra. Inhalation of a mixture containing fifty per cent. of carbon dioxide and fifty per cent. of oxygen was followed by an immediate fall of arterial pressure; which fall amounted, in twenty seconds, to eleven millimetres; in forty seconds, to forty-nine millimetres; in fifty seconds, to sixty-nine millimetres. Ten seconds later, exactly one minute after the commencement of

FIG. 10.



EXPERIMENT *A*.—Tracing showing effect of inhalation of carbonized acid gas upon the pulse in normal dog.

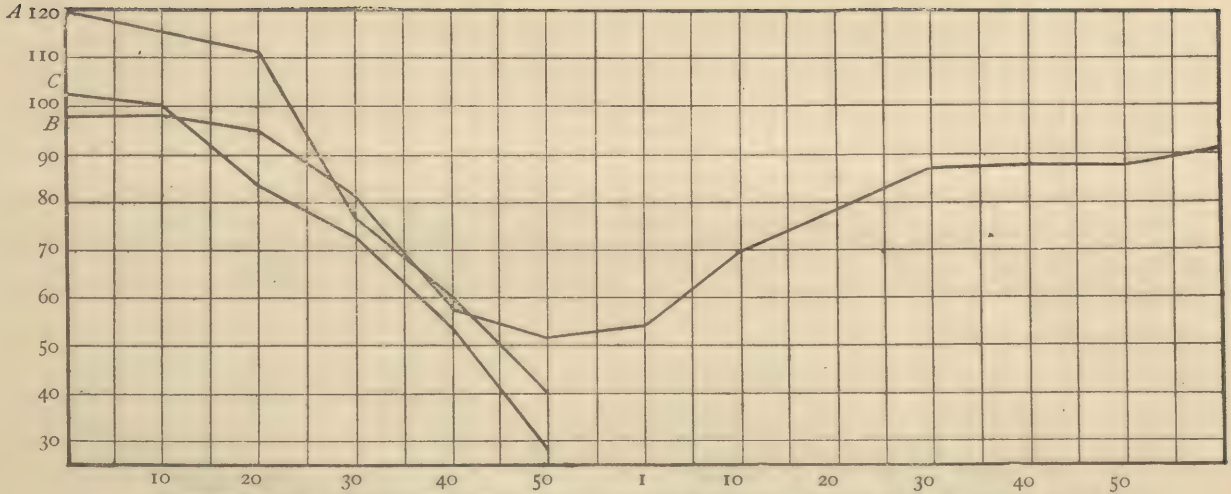
EXPERIMENT *B*.—Tracing showing effect upon the pulse after section of vagi.

the inhalation, the heart stopped, though respiration continued for several seconds.

In Experiment 29 (January 27, 1890) the spinal cord was cut in the extreme upper dorsal region; an inhalation of a mixture containing 66.6 of oxygen and 33.3 of carbonic acid was followed by an immediate fall of the arterial pressure, which fall, in twenty seconds, amounted to seventeen millimetres; in forty seconds, to forty millimetres. After this the pressure began to rise, so that in seventy seconds after the commencement of the inhalation it was twenty-eight millimetres below the norm, and a minute later it was only four millimetres below the norm. At this time the animal was allowed to recover himself and breathe ordinary air for fifteen minutes; at the end of this time the arterial pressure was a little higher than it had been at the beginning of the inhalation. Pure carbonic acid was then given; the fall of pressure was immediate and progressive until death, which occurred in a minute and a half; thus, in twenty seconds, the pressure fell twenty-four millimetres; in forty seconds, forty-nine millimetres; in fifty seconds, seventy-four millimetres.

In Experiment 30, after section of the cord below the first dorsal vertebra, an inhalation was administered containing fifty per cent. of ordinary air and fifty per cent. of carbon dioxide. Immediately after, violent struggles occurred in the anterior portion of the body, causing the blood-pressure temporarily to rise, so that in fifteen seconds after the beginning of the inhalation it was three millimetres above the norm; a rapid fall then took place, amounting in fifteen seconds to forty-five millimetres,

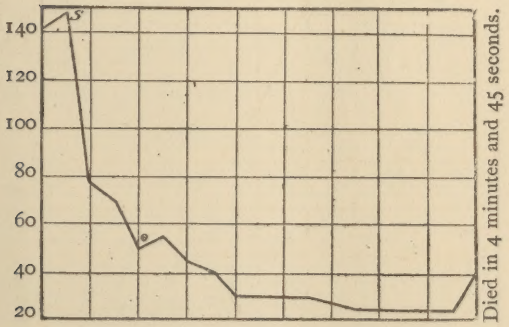
FIG. 11.



EXPERIMENT 29.—Blood-pressure tracings of C_2O and O, after section of spinal cord. *A*, mixture of C_2O and O, fifty per cent. of each. *B*, mixture of C_2O and O, thirty-three per cent. of first and sixty of second. *C*, pure C_2O.

in fifteen seconds more to seventy-four millimetres, in fifteen seconds more to ninety millimetres. After this the pressure, with one temporary exception due to struggles, slowly fell until, four minutes after the beginning of the inhalation, it was one hundred and eighteen millimetres below the norm; thirty seconds later the heart stopped.

FIG. 12.



EXPERIMENT 30.—Cord cut. Mixture of equal parts of air and C_2O. *S*, struggles. ⊙, convulsions.

The results of these three experiments are diagrammatically shown in the foregoing cuts.

These experiments prove that, after section of the spinal cord, carbonic acid is powerless, even when well diluted, to cause rise of the arterial pressure, and, as a corollary from this, that the rise of the arterial pressure, which is produced in the normal animal by inhalation of diluted carbonic acid, is due to stimulation of the vaso-motor centre in the medulla. The fall of pressure produced by strong carbonic acid is probably due to vaso-motor palsy.